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Titanium Tetraiodide-promoted Tandem Prins Reaction of Alkynes with Acetals: Synthesis of (*Z*,*Z*)-1,5-Diiodo-1,3,5-triarylpenta-1,4-dienes

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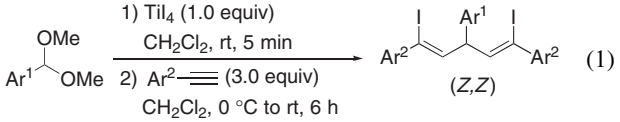
In the presence of titanium tetraiodide, a tandem Prins reaction of alkynes proceeded with acetals to give (*Z*,*Z*)-1,5-diiodo-1,3,5-triarylpenta-1,4-dienes in good yields, where an intriguing reversal of the stereoselectivity was observed among titanium tetrahalides.

Although the Prins reaction of alkenes with carbonyl compounds provides important C–C bond formations in a regio- and stereoselective manner, its alkyne analogs have not always been carried out readily.[1] This is due in part to further reactions of the resulting alkenes. We have recently described useful reactions using titanium tetraiodide, where the ability of titanium tetraiodide to iodinate and reduce organic molecules is responsible for the success of facile transformations.[2]

In an effort to utilize more effectively the iodination ability of titanium tetraiodide, we have already found the hydroiodination reaction of alkenes and alkynes with titanium tetraiodides.[3] The Aza-Prins reaction also proceeded using the *p*-tosylimine derived from ethyl glyoxylate.[4] This paper describes an intriguing tandem Prins reaction of alkynes promoted by titanium tetraiodide to give stereoselectively (*Z*,*Z*)-1,5-diiodo-1,3,5-triarylpenta-1,4-dienes (eq 1).



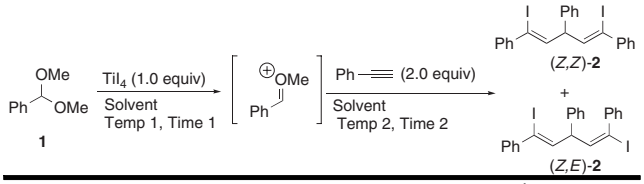
(1)

In 2002 Kabalka and co-workers reported an important Prins reaction of alkynes with aldehydes in the presence of titanium tetrachloride or tetrabromide to give the corresponding 1,5-dihalo-1,4-dienes with high (*Z*,*E*)-stereoselectivity.[5] We carried out similar reactions using acetals and titanium tetraiodide, and found that the reaction gave 1,5-diiodopenta-1,4-dienes with good (*Z*,*Z*)-selectivity, which contrasts to the results using titanium chloride or bromide. Results are summarized in Table 1.

Among the solvents screened, dichloromethane gave the desired Prins adduct in good yields. The best result was obtained when the reaction was carried out first mixing the acetal with titanium tetraiodide in dichloromethane at rt for 5 min, and then treatment of the whole mixture with alkyne at 0 °C to rt for 6 h to give the adduct **2** in 61% yield with a ratio of (*Z*,*Z*):(*Z*,*E*) = 86:14 (Entry 8). In order to improve the diastereoselectivity, we carried out a series of reactions in the presence of additives. Addition of bases (Na_2CO_3 and K_2CO_3), silver salts (AgOTf and $AgBF_4$), alkene (2-methyl-2-butene), and iodine did not noticeably improve the yield and diastereoselectivity. We then examined the ratios of reagents, and Table 2 summarizes the results.

As shown, increasing the ratio of alkyne improved the product yield, and when the reaction was carried out with 3 equiv of alkyne, the best diastereomer ratio of (*Z*,*Z*):(*Z*,*E*) = 91:9 was obtained (Entry 2). Under the best conditions a variety of *p*-substituted benzaldehyde dimethylacetals were subjected to the present Prins reaction, and Table 3 summarizes the results.

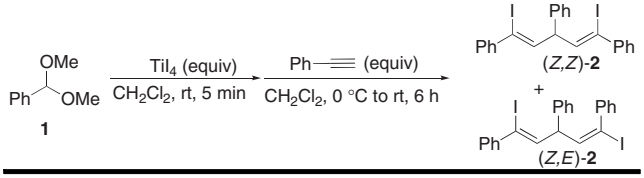
Table 1. Prins reaction of phenylacetylene with benzaldehyde dimethylacetal: comparison of reaction conditions[a]



Entry	Solvent	Temp 1 /°C	Time 1 /min	Temp 2 /°C	Time 2 /h	Yield[b] /%	Ratio[c] (*Z*,*Z*):(*Z*,*E*)
1	EtCN	rt	5	0	6	trace	—
2	THF	rt	5	0	6	1	100:0
3	PhMe	rt	5	0	6	4	23:77
4	CH_2Cl_2	rt	5	0	6	60	86:14
5	CH_2Cl_2	rt	30	0	6	32	78:22
6	CH_2Cl_2	rt	5	0 to rt	6	58	84:16
7	CH_2Cl_2	0	5	0 to rt	6	56	65:35
8[d]	CH_2Cl_2	rt	5	0 to rt	6	61	86:14
9[d]	CH_2Cl_2	rt	5	0 to rt	18	59	83:17

[a]The reaction was carried out according to the typical procedure (ref. 6).[9] [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Alkyne was added at 0 °C and then the reaction was carried out at rt in the dark.

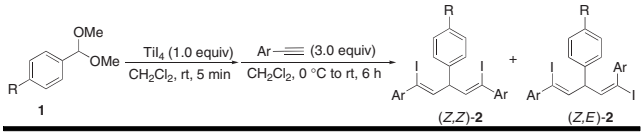
Table 2. Prins reaction of phenylacetylene with benzaldehyde dimethylacetal: comparison of amounts of titanium tetraiodide and alkyne[a]



Entry	TiI_4/equiv	Alkyne/equiv	Yield[b]/%	Ratio[c] (*Z*,*Z*):(*Z*,*E*)
1	1.0	2.5	71	86:14
2	1.0	3.0	68	91:9
3	1.0	3.5	64	70:30
4	1.25	3.0	70	81:19
5	1.5	3.0	76	73:27
6	2.0	3.0	76	69:31
7	2.5	3.0	67	69:31

[a]The reaction was carried out according to the typical procedure (ref. 6).[9] [b]Isolated yield. [c]Determined by ^{1}H NMR.

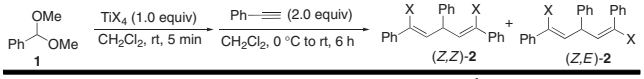
Table 3. Prins reaction of alkynes with acetals[a]



Entry	R	Ar	Yield[b]/%	Ratio[c] (*Z*,*Z*):(*Z*,*E*)
1	Me	Ph	57	55:44
2	MeO	Ph	40	40:60
3	Cl	Ph	62	74:26
4	NO_2	Ph	0	—
5	H	4-$MeOC_6H_4$	70	68:32
6	H	4-ClC_6H_4	57	40:52
7	H	4-BrC_6H_4	52	70:30

[a]The reaction was carried out according to the typical procedure (ref. 6).[9] [b]Isolated yield. [c]Determined by ^{1}H NMR.

Table 4. Prins reaction of alkynes with benzaldehyde dimethylacetal: comparison of TiX_4



Entry	X	Yield[a]/%	Ratio[b] (*Z*,*Z*):(*Z*,*E*)
1	F	0	—
2	Cl	67	4:96
3	Br	68	11:89

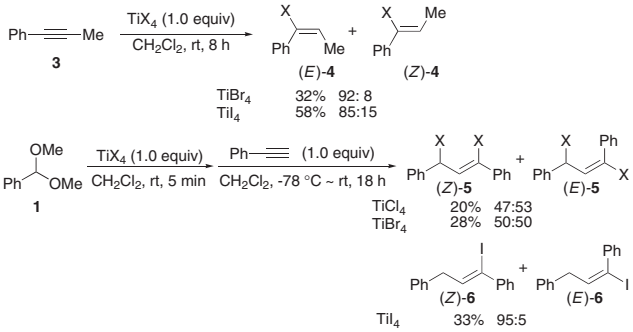
[a]Isolated yield. [b]Determined by ^{1}H NMR.

Regarding the acetals, electron-donating substituents decreased the diastereomer ratios, whereas chlorophenyl derivative recorded a slightly decreased diastereomer ratio (Entries 1 to 3). Among the alkynes studied here, an electron-donating methoxy derivative gave the highest yield although the best diastereoselectivity was obtained with simple phenylacetylene (Entry 6). We next examined the effects of the titanium halides. Table 4 summarizes the results.

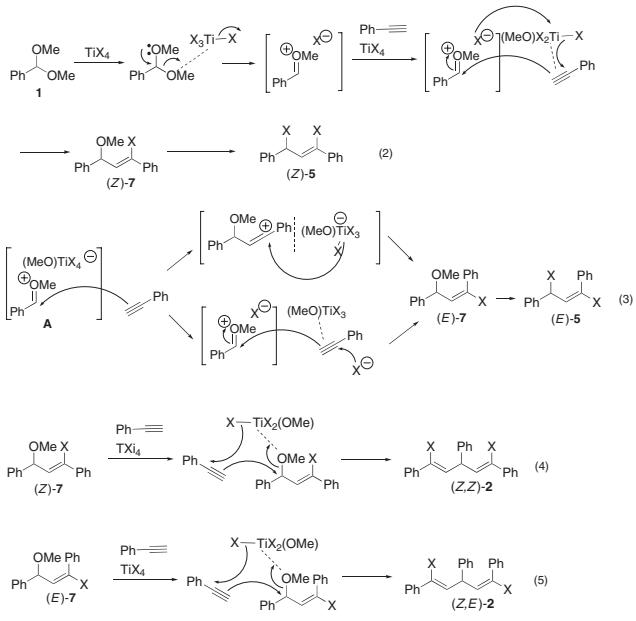
Although the reaction did not proceed with titanium tetrafluoride, reversal of the diastereoselectivity was observed in the cases with titanium tetrabromide and tetrachloride. In order to explain the stereoselectivity of the halotianation of alkynes, we first carried out hydroiodination and hydrobromination of 1-phenylpropyne, and Scheme 1 summarizes the results.

Both titanium tetrabromide and tetraiodide gave (*E*)-1-halo-1-phenylpropenes **4** as major products, indicating that the initial halotitanation in the absence of methoxide species proceeded in a *syn*-selective manner for both titanium halides. However, the reaction of the acetal with one equivalent of alkyne gave different results. While the reaction with titanium tetraiodide was stereoselective, giving (*Z*)-iodoalkene **6**,[7] that with titanium tetrabromide or tetrachloride gave an almost 1:1 mixtute of the (*Z*)- and (*E*)-isomers **5**. On the basis of these results the following mechanisms are proposed (Scheme 2).

A concerted mechanism might operate in the titanium tetraiodide promoted reactions, leading to the stereoselective formation of a (*Z*)-adduct **7** (eq 2), whereas formation of (*E*)-adduct **7** is explained by assuming involvement of a titanate species **A** which has a precedent in the tetrahydropyranyl ring-like transition state with titanium tetrabromide (eq 3).[8] For the



Scheme 1. Examination of stereochemistry.



Scheme 2. Plausible mechanism of the reaction.

formation of titanates, titanium tetrachloride and tetrabromide may be preferred to the iodide analog. Subsequent concerted second Prins reactions give (*Z*,*Z*)-1,5-dihalo-1,3,5-triarylpenta-1,4-diene with titanium tetraiodide (eq 4) and its (*Z*,*E*)-counterparts with chloro and bromo derivatives (eq 5).

In conclusion we have found that a stereoselective tandem Prins reaction proceeded with alkynes and acetals to give (*Z*,*Z*)-1,5-diiodo-1,3,5-triarylpenta-1,4-dienes using titanium tetraiodide, whereas their (*Z*,*E*)-counterparts were obtained with titanium tetrabromide or tetrachloride. The difference of the diastereoselectivity may be explained by assuming either a concerted cyclic mechanism or a separated ion pair model.

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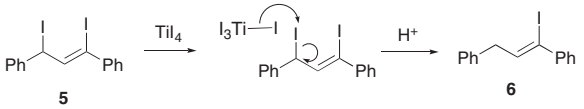
6 A typical procedure is as follows: To a suspension of TiI_4 (Soekawa Chemical Co., used after sublimation, 111 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) in a flask wrapped with aluminum foil was added a solution of benzaldehyde dimethylacetal (30.4 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at rt. After stirring at rt for 5 min, the mixture was cooled to 0 °C and to it was added a solution of phenylacetylene (61.3 mg, 0.60 mmol) in CH_2Cl_2 (1.0 mL). The mixture was allowed to stand at rt for 6 h with stirring. The reaction was quenched by the addition of sat. aq $NaHCO_3$ and aq $NaHSO_3$ (5%). The mixture was filtered through a Celite pad. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give a crude oil. Purification on silica gel TLC (hexane:AcOEt = 30:1, developed twice) gave (*Z*,*Z*)-1,5-diiodo-1,3,5-triphenylpenta-1,4-diene ((*Z*,*Z*)-**2**) (63.0 mg, 62%) and its (*Z*,*E*)-isomer (6.1 mg, 6%). (*Z*,*Z*)-**2**: pale yellow oil; $R_f = 0.43$ (hexane:AcOEt = 30:1 developed twice); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (t, $J = 8.7$ Hz, 1H), 6.25 (d, $J = 8.7$ Hz, 2H), 7.25–7.52 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.8, 106.8, 127.0, 127.6, 128.2, 128.6, 128.7, 128.9, 138.0, 140.5, 142.9; IR (neat): 3056, 3025, 1596, 1488, 1442, 1299, 1236, 1207, 1182, 1068, 1029, 999, 897, 854, 796, 756, 693, 625, 614, 555 cm^{-1}; HRMS (EI) *m*/*z*: Calcd for $C_{23}H_{18}I_2$ $(M)^+$ 547.9498, found 547.9492. (*Z*,*E*)-**2**: pale yellow oil; $R_f = 0.52$ (hexane:AcOEt = 30:1 developed twice); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (dd, $J = 9.2$, 10.0 Hz, 1H), 6.07 (d, $J = 9.2$ Hz, 1H), 6.73 (d, $J = 10.0$ Hz, 1H), 7.24–7.46 (m, 15H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 97.7, 105.8, 127.0, 127.3, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 137.8, 140.6, 141.1, 141.4, 142.7; IR (neat): 3055, 3025, 1596, 1487, 1442, 1308, 1229, 1179, 1068, 1028, 898, 835, 798, 758, 695, 634, 611, 556 cm^{-1}; HRMS (EI) *m*/*z*: Calcd for $C_{23}H_{18}I_2$ $(M)^+$ 547.9498, found 547.9490. For the assignment of the alkene geometries, see: D. P. Curran, D. Kim, *Tetrahedron* **1991**, *47*, 6171; P. J. Kropp, S. D. Crawford, *J. Org. Chem.* **1994**, *59*, 3102; Y. Gao, K. Harada, T. Hata, H. Urabe, F. Sato, *J. Org. Chem.* **1995**, *60*, 290.

7 The compound **6** may be obtained by reduction of the allyl iodide **5** with titanium tetraiodide.



5 **6**

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9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

